42. (Amended) A method of treating acquired immunodeficiency syndrome, comprising administering to a subject in need thereof an immunotoxin according to claim 30.

REMARKS

Claims 21-42 are pending in the present application and stand rejected under 35 U.S.C. § 103. Claims 21-29 and 34-36 are cancelled herein without prejudice. Thus, claims 30-33 and 37-42 are under consideration. Claims 30-33 and 38-42 are amended herein. Attached hereto as Appendix A is a marked-up version of the amended claims, showing the amendments made thereto.

Claim 30 is amended to be an independent claim, thus incorporating the language of claim 21, "comprising a single chain variable region of an anti-CD3 antibody linked to a toxin moiety." Support for this amendment is found in claims 1 and 3 as originally filed. Claim 30 is further amended to include the language, "and wherein the diphtheria toxin moiety is a truncation of native diphtheria toxin at the carboxy terminus." Support for this amendment can be found at page 9, lines 15-16, page 13, lines 13-15; page 40, lines 28-32; and Example 9, pages 38-54.

Claim 31-33 and 38-42 are amended to recite "the" instead of "a" where there is antecedent support for the noun that follows and/or amended to depend on a pending claim,

rather than a cancelled claim. These are not narrowing amendments and are made merely for purposes of simplification.

The Examiner has maintained the rejection of all pending claims under 35 U.S.C. § 103, as allegedly obvious based on Chaudhary et al., Neville et al., Hirsch et al., and Whitlow et al., and, optionally, further in view of Youle *et al.* Applicants respectfully traverse these rejections.

The Examiner states, "[T]he instantly disclosed and claimed DT390 appears to be obvious over the DT388 of Chaudhary et al, absent a showing of unobvious properties." Office Action dated January 18, 2002, p. 3. Applicants respectfully point out that DT390 is *not* claimed in the present invention and that it is legal error to find each element of a combination requires unobvious properties if the combination itself (i.e., a toxin moiety and an antibody moiety) has unobvious properties. In the present application, it is the combination of the truncated diphtheria toxin moiety *and* the single chain variable region of the anti-CD3 antibody that is claimed in independent claims 30 and 37, and it is this combination that has unobvious properties.

In the declaration, attached hereto as Appendix B, Dr. Neville provides data and two manuscripts that indicate the relative unpredictability of the properties of imunotoxin fusion proteins. The single chain variable regions of various CD3 antibodies in immunotoxin contructs result in substantially different toxicities, despite comparable affinities in the parental antibodies. Even now, one skilled in the art cannot predict the effectiveness of T-cell depletion by a new anti-CD3 antibody single chain variable region combined with a truncated diphtheria moiety.

See Exhibit B, paragraph 6 ("DT390sFv(UCHT1) is a superior anti-T cell immunotoxin *but the reason for this superiority has not yet been fully elucidated.* DT390sFv(UCHT1) produces profound (>1.5 logs) *in vivo* depletion of resting T cells . . ., whereas similar DT390sFv immunotoxins fail to produce a comparable depletion.") (emphasis added). It is only by constructing the immunotoxin fusion protein and assessing its function that one skilled in the art can ascertain how effective a specific immunotoxin fusion protein will be. Dr. Neville indicates in his declaration that the relevant science has still not reached a level such that the amount of T-cell depleting function of an immunotoxin fusion protein with a single chain variable region antibody moiety is predictable. Thus, at the time the claimed immunotoxin was made, one skilled in the art certainly could not have predicted the specific fusion immunotoxin would be vastly superior in T cell depletion. It was only through trial and error that the inventors, or others skilled in the art, could have determined that the claimed imunotoxin fusion protein was vastly superior.

None of the cited references either teach the claimed immunotoxin fusion protein or suggest its surprising effectiveness. Deficiencies in the prior art references are discussed in detailed in the Amendment dated April 3, 2001. Applicants respectfully ask the Examiner to consider these deficiencies in the prior art, along with the attached declaration indicating the surprising effectiveness of the claimed immunotoxins. The cited references, at best, create an incentive to try, without any reasonable expectation of improved T cell depletion. "'Obvious to try' [however] has long been held not to constitute obviousness. *In re Farrell*, 853 F.2d 894,

903, 7 U.S.P.Q.2d 1673, 1680-81 (Fed. Cir. 1988). A general incentive does not make obvious a particular result . . . ." *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995).

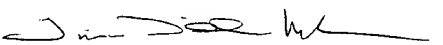
Furthermore, in the case of biological macromolecules, the Federal Circuit has held that such molecules are not obvious merely because the methods of making such molecules are known. In *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995), the court stated, "[E]ven if, as the examiner stated, the existence of general cloning techniques, coupled with knowledge of a protein's structure, might have provided motivation to prepare a cDNA or made it obvious to prepare a cDNA, that does not necessarily make obvious a particular claimed cDNA. . . ." *Id.* at 1559. The same logic applies in the present case. Even if the cited references teach how to make immunotoxins or various elements of a specific immunotoxin, they cannot render obvious the specific immunotoxin as claimed. Thus, in the absence of a likelihood of effectiveness of a given immunotoxin, the availability of methods to make those immunotoxins does not render obvious the specific highly superior immunotoxin.

Applicants respectfully request that the amendments be entered and the remarks considered. Pursuant to these amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. In any event, the amendments put the claims in better form for appeal, should the claims not be allowed. The PTO is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of the application to issue.

Payment in the amount of $110.00 is to be charged to a credit card and such payment is authorized by the signed, enclosed document entitled: Credit Card Payment Form PTO-2038. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees that may be required to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.



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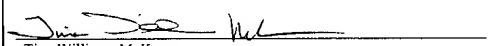
I hereby certify that this correspondence as well as anything indicated as being attached or enclosed is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Box AF, Commissioner for Patents, Washington, D.C. 20231, on the date shown below.



Tina Williams McKeon

May 7, 2002

Date

APPENDIX A
MARKED-UP VERSION OF THE AMENDED CLAIMS

30. A fusion immunotoxin comprising a single chain variable region of an anti-CD3 antibody linked to a toxin moiety [according to claim 28], wherein the anti-CD3 antibody is UCHT1 and wherein the diphtheria toxin moiety is a truncation of native diphtheria toxin at the carboxy terminus.

31. [A] The fusion immunotoxin according to claim 30, wherein the toxin moiety is DT390.

32. [A] The fusion immunotoxin according to claim [21] 31, comprising DT390 linked via its carboxy terminus, optionally via a linker, to the single chain variable region of the anti-CD3 antibody.

33. [A] The fusion immunotoxin according to claim 32, wherein the single chain variable region of the anti-CD3 antibody comprises the variable light domain linked via its carboxy terminus to the variable heavy domain, optionally via a linker.

38. A method for inhibiting rejection of transplanted tissue or organs, comprising administering to a subject in need thereof an immunotoxin according to claim [21] 30.

39. A method for treating an autoimmune disease, comprising administering to a subject in need thereof an immunotoxin according to claim [21] 30.

40. A method of treating T cell leukemias or lymphomas, comprising administering to a subject in need thereof an immunotoxin according to claim [21] 30.

41. A method of treating graft-versus-host disease, comprising administering to a subject in need thereof an immunotoxin according to claim [21] 30.

42. A method of treating acquired immunodeficiency syndrome, comprising administering to a subject in need thereof an immunotoxin according to claim [21] 30.